

Safety and Efficacy of Eplerenone in Patients at High Risk for Hyperkalemia and/or Worsening Renal Function

Analyses of the EMPHASIS-HF Study Subgroups (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure)

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Objectives

The study sought to investigate the safety and efficacy of eplerenone in patients at high risk for hyperkalemia or worsening renal function (WRF) in EMPHASIS-HF, a trial that enrolled patients at least 55 years old with heart failure and reduced ejection fraction (HF-REF), in New York Heart Association (NYHA) functional class II and with an estimated glomerular filtration rate (eGFR) >30 ml/min/1.73 m² and serum potassium <5.0 mmol/l. Patients were receiving optimal therapy and most had been hospitalized for a cardiovascular reason within 180 days of inclusion.

Background

Underuse of eplerenone in patients with HF-REF may be due to fear of inducing hyperkalemia or WRF in high-risk patients.

Methods

This was a pre-specified analysis of subgroups of patients at high risk of hyperkalemia or WRF (patients ≥ 75 years of age, with diabetes, with eGFR <60 ml/min/1.73 m², and with systolic blood pressure $<$ median of 123 mm Hg), examining the major safety measures (potassium >5.5 , >6.0 , and <3.5 mmol/l; hyperkalemia leading to study-drug discontinuation or hospitalization; and hospitalization for WRF) as well as the primary outcome (hospitalization for HF or cardiovascular mortality).

Results

In all high-risk subgroups, patients treated with eplerenone had an increased risk of potassium >5.5 mmol/l but not of potassium >6.0 mmol/l, and of hospitalization for hyperkalemia or discontinuation of study medication due to adverse events. Eplerenone was effective in reducing the primary composite endpoint in all subgroups.

Conclusions

In patients with chronic HF-REF, in NYHA functional class II, and meeting specific inclusion and exclusion criteria, including an eGFR >30 ml/min/1.73 m² and potassium <5.0 mmol/l, eplerenone was both efficacious and safe when carefully monitored, even in subgroups at high risk of developing hyperkalemia or WRF. (A Comparison Of Outcomes In Patients In New York Heart Association [NYHA] Class II Heart Failure When Treated With Eplerenone Or Placebo In Addition To Standard Heart Failure Medicines [EMPHASIS-HF Study]; NCT00232180) (J Am Coll Cardiol 2013;62:1585–93) © 2013 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

ACE-I	= angiotensin-converting enzyme inhibitor
ARB	= angiotensin receptor blocker
BB	= beta-adrenergic receptor blocking agent
CI	= confidence interval
CKD	= chronic kidney disease
DM	= diabetes mellitus
eGFR	= estimated glomerular filtration rate
HF-REF	= heart failure with a reduced left ventricular ejection fraction
HR	= hazard ratio
MRA	= mineralocorticoid receptor antagonist
SBP	= systolic blood pressure
WRF	= worsening renal function

Mineralocorticoid receptor antagonists (MRAs) added to standard therapy including an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and a beta-adrenergic receptor blocking agent (BB) reduce mortality as well as hospitalization for heart failure (HF) in patients with a reduced left ventricular ejection fraction (HF-REF), irrespective of the severity of symptoms (1,2), and in patients with reduced left ventricular ejection fraction and symptoms of HF after myocardial infarction (3). Mineralocorticoid receptor antagonists, therefore, have a pivotal place in the management of HF-REF (4) but, in comparison with ACE-I (or ARBs) and BBs, their use remains suboptimal (5). The reluctance of many clinicians to use a MRA in patients with HF-REF may

in part be due to the belief that the large clinical trials, such as RALES (Randomized Aldactone Evaluation Study) (1), EPHEsus (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.) (3), and EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure) (2), largely excluded high-risk patients, particularly those susceptible to hyperkalemia, worsening renal function (WRF), or both.

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The aim of this analysis was to evaluate the safety and efficacy of the MRA eplerenone (25 to 50 mg/day) in pre-specified high-risk subgroups of this type, namely patients age ≥ 75 years, with diabetes mellitus, chronic kidney disease (CKD; i.e., an estimated glomerular filtration rate

[eGFR] < 60 ml/min/1.73 m²), and systolic blood pressure (SBP) $<$ median (123 mm Hg).

Methods

The design (6) and results (2) of the EMPHASIS-HF study have been published.

Patient selection. Patients included were at least 55 years of age; were in New York Heart Association functional class II; had a left ventricular ejection fraction $< 30\%$ (or if between 30% and 35%, the QRS duration had to be > 130 ms); were treated with the recommended or maximally tolerated dose of an ACE-I or an ARB and a BB (unless contraindicated); and had been hospitalized for a cardiovascular reason within the past 6 months (or had a B-type natriuretic peptide level > 250 pg/ml or N-terminal pro-B-type natriuretic peptide > 500 pg/ml in males and 750 pg/ml for females).

Patients with an eGFR < 30 ml/min/1.73 m², need for a potassium sparing diuretic, or any other significant comorbid condition was excluded.

All trial endpoints, including hospitalization for WRF and for hyperkalemia were pre-specified and adjudicated by an independent Critical Event Committee. Each center's Ethics Committee approved the trial and all patients provided written informed consent.

Study procedure. Eplerenone or matching placebo was started at a dose of 25 mg once daily (or if the eGFR was 30 to 49 ml/min/1.73 m², at a dose of 25 mg every other day) and increased to 50 mg once daily at 4 weeks, provided the serum potassium was no more than 5.0 mmol/l (or if the eGFR was 30 to 49 ml/min/1.73 m² at baseline to 25 mg daily). Thereafter, the serum potassium was measured every 4 months and investigators were instructed to reduce the dose of the study drug if the serum potassium was 5.5 to 5.9 mmol/l and to withhold the study drug if the serum potassium was 6.0 mmol/l or more. Serum potassium was checked within 72 h of stopping study drug and restarted only if the serum potassium was < 5.0 mmol/l. Serum potassium was measured at screening visit, Week 1, Week 4, every 4 months from Month 5 to Month 37, and every 6 months starting at Month 42 until the patient's final visit.

High-risk subgroups. The pre-specified high-risk subgroups were patients ≥ 75 years of age, those with diabetes mellitus, CKD (i.e., an eGFR < 60 ml/min/1.73 m²), and subjects with an SBP < 123 mm Hg (median) at baseline.

Study outcomes. The pre-specified safety outcomes included serum potassium > 5.5 , > 6.0 , and < 3.5 mmol/l; hyperkalemia leading to study drug discontinuation; hospitalization for hyperkalemia and hospitalization for WRF; change in eGFR; and the primary efficacy outcome (hospitalization for HF or death from cardiovascular causes) were also reported.

Statistical analysis. The criteria for high-risk subgroups were pre-specified in the statistical analysis plan. The

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following data are summarized by study treatment for each of the high-risk subgroups:

1. Demographics, medical history, and relevant baseline laboratory measurements and medications (summarized using descriptive statistics).
2. Hospitalizations for hyperkalemia and for WRF were analyzed using Cox proportional hazards models. The incidence of serum potassium above or below the pre-specified thresholds during the study were compared using Fisher exact test. Change in eGFR between baseline and the final visit was analyzed using an analysis of covariance model with baseline eGFR as a covariate. We also examined for interactions between baseline subgroup and the effect of treatment on potassium and eGFR using the Zelen's test and the analysis of covariance model including the interaction term, respectively.

The adverse event data and study medication data including percent of subjects on highest dose (50 mg QD) and mean dose at Month 5 visit, and subject discontinuation are also summarized. Statistical comparisons between treatment groups were performed using 2-sample *t* tests for mean dose at Month 5 visit, and Fisher exact test for study discontinuation due to adverse events. The BP change from baseline is also presented by baseline SBP < median and ≥ median subgroups.

3. The efficacy analyses on the primary endpoint (death from cardiovascular causes or hospitalization for HF) are performed using a Cox proportional hazards models including treatment, subgroup, and the treatment-by-subgroup interaction. Additionally, the corresponding Kaplan-Meier plots are presented by subgroups.

Results

The baseline characteristics of those patients randomized to placebo or eplerenone in the EMPHASIS-HF study overall, and in the high-risk subgroups, are presented in Table 1. There were no striking clinical differences between the different high-risk subgroups and the overall population, except those reflected by the defining characteristic of the subgroup.

At the Month 5 visit, after completion of the dose-adjustment phase 61.3% of patients assigned to receive eplerenone in the overall study population were taking the highest dose (50 mg daily); the corresponding proportion in the overall placebo group was 66.3%. Among the patients in overall population taking the study drug at the Month 5 visit, the mean ± SD doses in the eplerenone and placebo groups, respectively, were 39.5 ± 13.6 mg and 41.1 ± 12.7 mg. Neither the proportion of patients taking the highest dose (except for patients with CKD), nor the mean dose of study drug at the Month 5 visit differed between

Table 1 Baseline Characteristics

Characteristics	EMPHASIS-HF Study Population		Age ≥75 yrs	Diabetes Mellitus	eGFR <60 ml/min/1.73 m ²	Baseline Systolic Blood Pressure ≤ Median (123 mm Hg)
	Eplerenone Group (n = 1,364)	Placebo Group (n = 1,373)	Eplerenone Group (n = 330)	Eplerenone Group (n = 459)	Eplerenone Group (n = 439)	Eplerenone Group (n = 682)
Age, yrs	68.7 ± 7.7	68.6 ± 7.6	79.1 ± 3.5	68.1 ± 7.4	71.1 ± 7.5	68.2 ± 7.6
Female	309 (22.7)	301 (21.9)	78 (23.6)	103 (22.4)	119 (27.1)	148 (21.7)
Systolic blood pressure, mm Hg	124 ± 17	124 ± 17	127.07 ± 17.1	125.23 ± 17.1	122.23 ± 16.9	110.51 ± 9.1
Diastolic blood pressure, mm Hg	75 ± 10	75 ± 10	73.67 ± 10.5	74.64 ± 10.3	73.19 ± 10.9	69.32 ± 8.7
Left ventricular ejection fraction, %	26.2 ± 4.6	26.1 ± 4.7	26.72 ± 4.3	26.44 ± 4.7	26.39 ± 4.7	25.74 ± 4.8
Hospitalization for heart failure	714 (52.3)	726 (52.9)	169 (51.2)	234 (51.0)	254 (57.9)	394 (57.8)
Hypertension	910 (66.7)	909 (66.2)	250 (75.8)	348 (75.8)	304 (69.2)	374 (54.8)
Myocardial infarction	686 (50.3)	695 (50.6)	188 (57.0)	249 (54.2)	241 (54.9)	352 (51.6)
Diabetes mellitus	459 (33.7)	400 (29.1)	97 (29.4)	459 (100.0)	167 (38.0)	211 (30.9)
Serum creatinine, mg/dl	1.14 ± 0.30	1.16 ± 0.31	1.22 ± 0.3	1.17 ± 0.3	1.44 ± 0.3	1.16 ± 0.3
eGFR, ml/min/1.73 m ² of body surface area	71.2 ± 21.9	70.4 ± 21.7	63.99 ± 20.0	69.27 ± 22.0	48.59 ± 7.9	68.77 ± 20.7
eGFR rate <60 ml/min/1.73 m ²	439 (32.2)	473 (34.5)	151 (45.8)	167 (36.4)	439 (100.0)	246 (36.1)
Serum potassium, mmol/l	4.3 ± 0.4	4.3 ± 0.4	4.30 ± 0.4	4.34 ± 0.4	4.36 ± 0.4	4.30 ± 0.4
Diuretic	1,150 (84.3)	1,176 (85.7)	286 (86.7)	408 (88.9)	400 (91.1)	592 (86.8)
ACE inhibitor	1,068 (78.3)	1,055 (76.8)	266 (80.6)	340 (74.1)	342 (77.9)	551 (80.8)
ARB	261 (19.1)	266 (19.4)	85 (25.8)	138 (30.1)	124 (28.3)	166 (24.3)
ACE inhibitor, ARB, or both	1,282 (94.0)	1,275 (92.9)	316 (95.8)	439 (95.6)	419 (95.4)	649 (95.2)
Beta-blocker	1,181 (86.6)	1,193 (86.9)	286 (86.7)	399 (86.9)	387 (88.2)	587 (86.1)

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate.

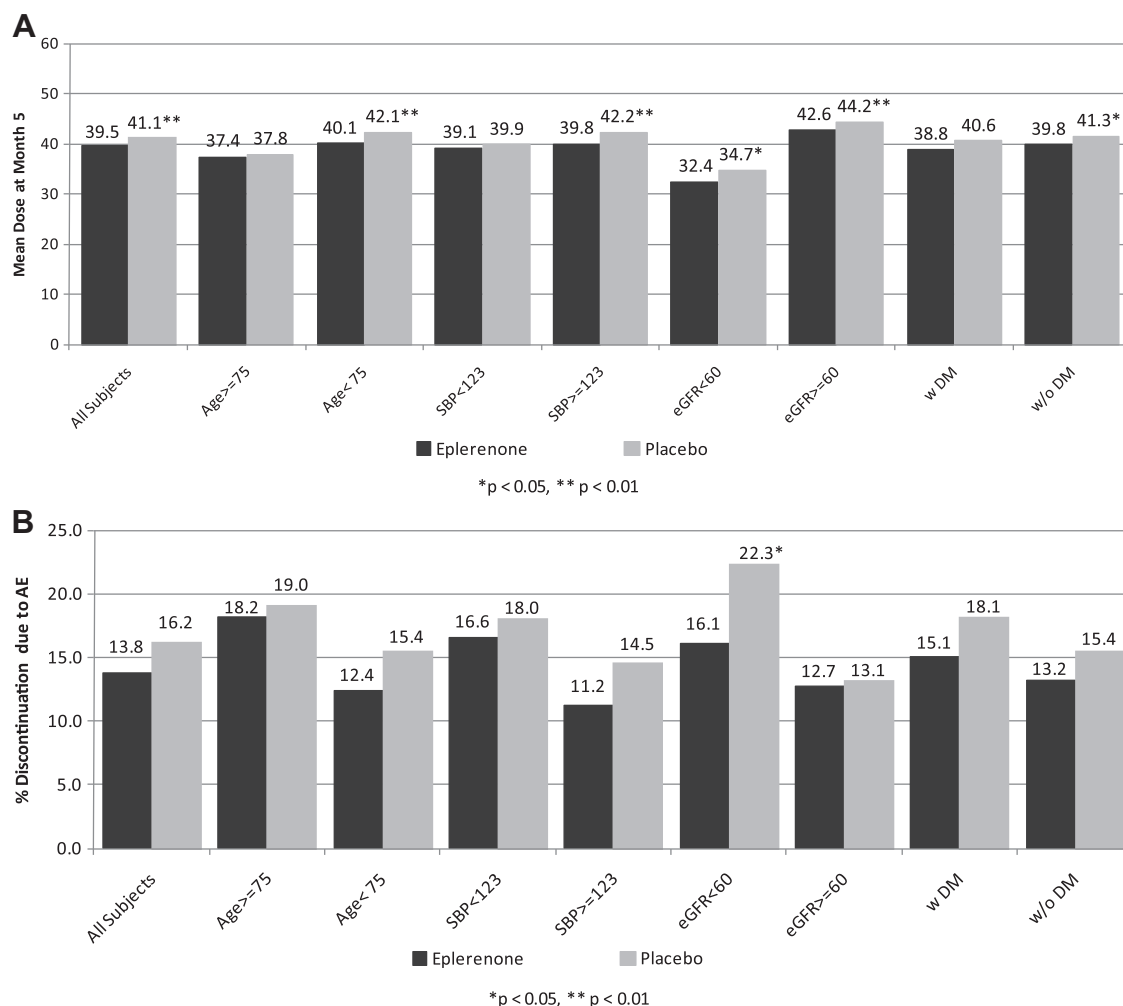


Figure 1 Mean Dose of Study Drug and Discontinuation of Study Drug Due to Adverse Event

(A) Bars for mean dose of study drug (eplerenone vs. placebo) at Month 5 visit in overall study population and in each high-risk subgroup. (B) Bars for discontinuation of study drug (eplerenone vs. placebo) due to adverse event at Month 5 visit in overall study population and in each high-risk subgroup. DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure.

eplerenone and placebo groups in each high-risk subgroups (Fig. 1A).

At the trial cutoff date, in the overall population, the study drug had been stopped, due to adverse event (at least 1 adverse event leading to drug being stopped), in 188 patients (13.8%) receiving eplerenone and 222 patients (16.2%) receiving placebo.

The number of patients with study drug stopped due to adverse events was evenly distributed within and among the study high-risk subgroups in patients age ≥ 75 years (60 of 330 [18.2%] in eplerenone vs. 62 of 327 [19.0%] in placebo), in patients with SBP < 123 mm Hg (111 of 669 [16.6%] in eplerenone vs. 122 of 679 [18.0%] in placebo), in patients with CKD (70 of 436 [16.1%] in eplerenone vs. 105 of 471 [22.3%] in placebo), and in patients with diabetes mellitus (69 of 457 [15.1%] in eplerenone vs. 72 of 398 [18.1%] in

placebo). Interestingly, in patients with CKD (eGFR < 60 ml/min/1.73 m²), there were fewer patients in eplerenone group who had their treatment stopped due to an adverse event or due to any other reason than in placebo group (Fig. 1B).

The principal safety outcomes, change in eGFR and the primary efficacy outcome in the overall EMPHASIS-HF study population and in each of the high-risk subgroups, are summarized in Table 2 and Figure 2.

Safety outcomes. Serum potassium > 5.5 and > 6.0 mmol/l occurred preferentially during the first 18 months after study drug (eplerenone and placebo) initiation. After initiation of the study drug, a serum potassium level > 5.5 mmol/l occurred at a median of 162.5 (range, 4 to 1,032) days in the eplerenone group compared with 235.0 (range, 7 to 1,008) days in the placebo group. Serum potassium > 6.0 mmol/l

Table 2 Primary Outcome and Major Safety Issues

	EMPHASIS-HF Study Population				Age ≥75 yrs		Diabetes Mellitus		eGFR <60 ml/min/1.73 m ²		Baseline Systolic Blood Pressure < Median (123 mm Hg)	
	Eplerenone Group (n = 1,364)	Placebo Group (n = 1,373)	Eplerenone Group (n = 330)	Placebo Group (n = 327)	Eplerenone Group (n = 459)	Placebo Group (n = 400)	Eplerenone Group (n = 439)	Placebo Group (n = 473)	Eplerenone Group (n = 669)	Placebo Group (n = 683)		
Outcome												
Hospitalization for heart failure or death for cardiovascular	249 (18.3%)	356 (25.9%) [†]	78 (23.6%)	107 (32.7%) [†]	99 (21.7%)	141 (35.2%) [‡]	107 (24.4%)	163 (34.5%) [‡]	138 (20.6%)	201 (29.4%) [‡]		
Serum K ⁺ >5.5 mmol/l	158/1,336 (11.8%)	96/1,340 (7.2%) [‡]	40/322 (12.4%)	21/318 (6.6%)*	63/447 (14.1%)	33/387 (8.5%) [†]	70/422 (16.6%)	43/461 (9.3%) [†]	72/658 (10.9%)	48/660 (7.3%)*		
Serum K ⁺ >6.0 mmol/l	33/1,336 (2.5%)	25/1,340 (1.9%)	7/322 (2.2%)	4/318 (1.3%)	17/447 (3.8%)	8/387 (2.1%)	8/422 (1.9%)	15/461 (3.3%)	14/658 (2.1%)	16/660 (2.4%)		
Change in eGFR from baseline to final visit (Mean (SD))	−3.18 (18.4)	−1.29 (18.2)*	−5.29 (17.6)	−4.07 (15.4)	−4.94 (17.4)	−2.93 (18.9)	2.04 (17.0)	4.15 (14.9)	−1.31 (17.3)	−0.07 (17.5)		

Difference between eplerenone and placebo groups within different subgroups: *p ≤ 0.05; †p ≤ 0.001; ‡p ≤ 0.0001. Abbreviations as in Table 1.

occurred at 276 (range, 4 to 987) days in the eplerenone group and 235.0 (range, 7 to 596) days in the placebo group.

Of 150 patients receiving eplerenone who had potassium >5.0 mmol/l at Week 4, 141 (94.0%) did not have their study drug dose increased, as per protocol. For comparison, of 94 patients receiving placebo who had potassium >5.0 mmol/l at Week 4, and 83 (88.3%) did not have their study drug dose increased.

Patients ≥75 years of age. There was an increase in the proportion of older patients with a follow-up potassium >5.5 mmol/l in those treated with eplerenone compared with placebo, 40 (12.4) versus 21 (6.6), p = 0.02, but there was no difference in the proportion with a potassium >6.0 mmol/l, 7 (2.2) versus 4 (1.3), p = 0.55. There was no increase in any other safety outcome with eplerenone. However, the reduction in SBP between baseline and the final visit was greater in the eplerenone group, −4.75 (18.8) versus −0.70 (16.5) mm Hg, p = 0.03, compared with the placebo group.

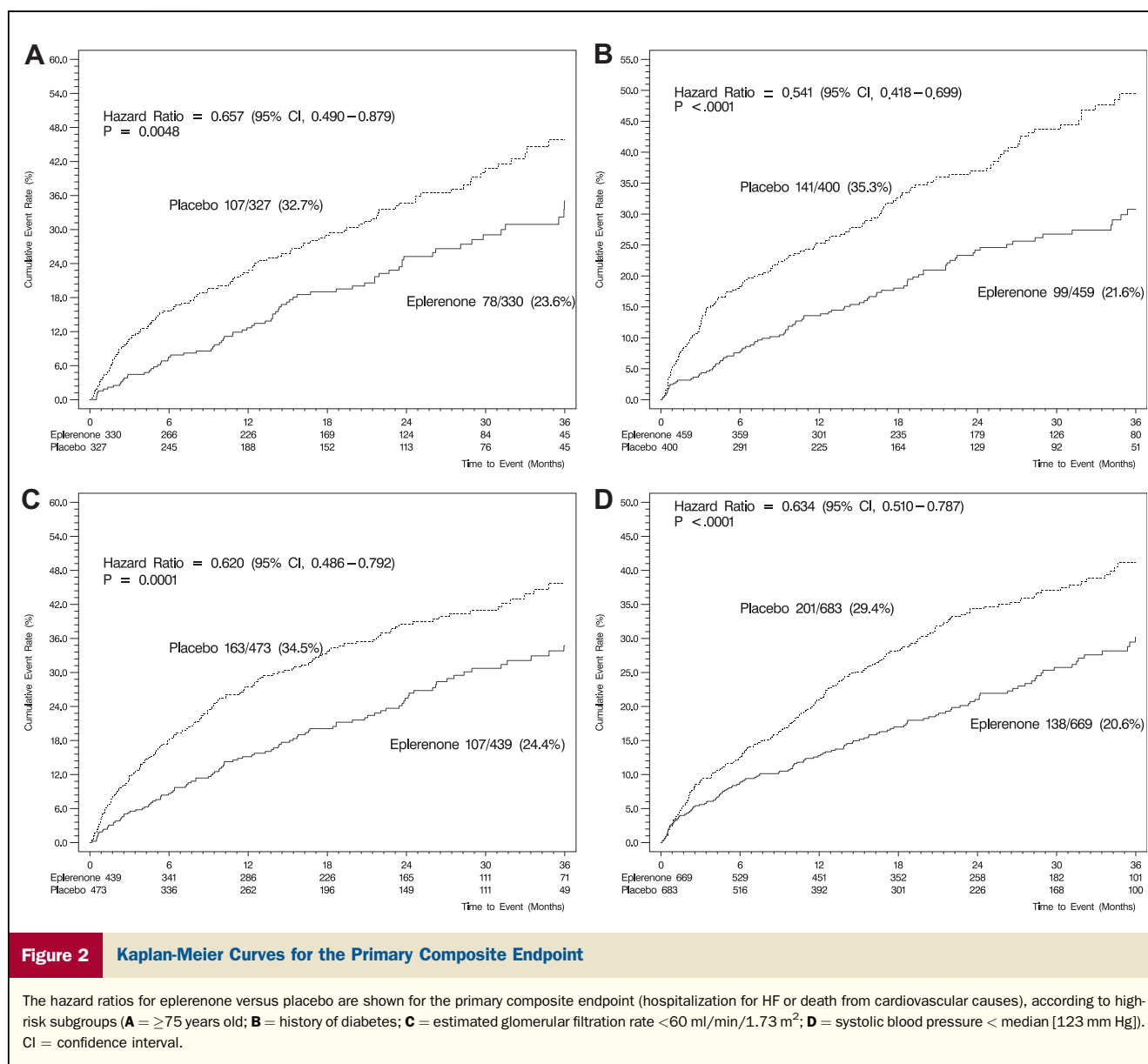
Furthermore, age (<75 vs. ≥75 years) did not modify the effect of eplerenone on the risk of severe hyperkalemia (interaction p = 0.64) or of change in eGFR from baseline to final visit (interaction p = 0.5071).

Patients with diabetes mellitus. There was an increase in the incidence of potassium >5.5 mmol/l with eplerenone in patients with diabetes, 63 (14.1) versus 33 (8.5) on placebo, p = 0.01. However, none of the other safety outcomes were increased in the eplerenone group, especially in the proportion with a serum potassium >6.0 mmol/l, 17 (3.8) versus 8 (2.1) on placebo, p = 0.16, and no more patients discontinued eplerenone for hyperkalemia in diabetes versus no-diabetes patients (interaction p = 0.12).

Patients with CKD (i.e., an eGFR <60 ml/min/1.73 m²). There was an increase in the incidence of potassium >5.5 mmol/l with eplerenone in patients with CKD, 70 (16.6) versus 43 (9.3) on placebo, p = 0.002. There was no increase in any other safety outcome with eplerenone, including in the proportion with a serum potassium >6.0 mmol/l, 8 (1.9) versus 15 (3.3) on placebo, p = 0.29.

Furthermore, there was actually a decrease in incident potassium >6.0 mmol/l, 8 (1.9) versus 25 (2.74), p = 0.01, but an increase in hyperkalemia leading to treatment discontinuation, 5 (1.15) versus 10 (1.08), p = 0.01, in eplerenone patients with CKD compared with patients without CKD.

Patients with below median SBP (<123 mm Hg). There was an increase in the incidence of potassium >5.5 mmol/l in patients with a SBP <123 mm Hg, 72 (10.9) versus 48 (7.3) on placebo, p = 0.02. There was no increase in any other safety outcome with eplerenone, especially in the proportion with a serum potassium >6.0 mmol/l, 14 (2.1) versus 16 (2.4) on placebo, p = 0.85. Interestingly, there was no increase in the incidence of serum potassium >5.5 nor >6.0 mmol/l with eplerenone in patients in the lowest quartile of baseline SBP (<110 mm Hg) and in patients with SBP between lowest quartile and median (between 110 and 123 mm Hg).



The mean decrease in SBP associated with the use of eplerenone in the EMPHASIS-HF study was 2 mm Hg overall. In patients with a SBP below the median of 123 mm Hg, SBP pressure increased on average by 4.96 (16.0) mm Hg in the eplerenone group versus 5.98 (16.2) mm Hg in the placebo group ($p = 0.19$). In patients with SBP \geq median (123 mm Hg) there was a significantly higher decrease in SBP in the eplerenone group as compared with the placebo group, -9.6 (16.8) mm Hg versus -6.27 (15.9) mm Hg, $p < 0.001$.

Furthermore, SBP (< 123 vs. ≥ 123 mm Hg) did not modify the effect of eplerenone on the risk of severe hyperkalemia ($p = 0.10$) or of change in eGFR from baseline to final visit ($p = 0.66$).

Primary efficacy outcome. Eplerenone was effective at reducing the risk of cardiovascular death or HF

hospitalization in the high-risk subgroups, which is consistent with result in the overall, the EMPHASIS-HF study population (hazard ratio [HR]: 0.63; 95% confidence interval [CI]: 0.54 to 0.74; $p < 0.001$).

Correspondingly, the HR for the primary outcome in the eplerenone group as compared with the placebo group was 0.66 (95% CI: 0.54 to 0.80; $p < 0.0001$) in patients < 75 years of age, 0.72 (95% CI: 0.58 to 0.88; $p = 0.002$) in patients without diabetes, 0.69 (95% CI: 0.56 to 0.86; $p = 0.0008$) in patients without CKD, and 0.68 (95% CI: 0.53 to 0.87; $p = 0.002$) in patients with SBP \geq median. All interaction tests were not significant.

The HR for the primary outcome in the eplerenone group as compared with the placebo group was 0.66 (95% CI: 0.49 to 0.88; $p = 0.005$) in patients ≥ 75 years of age, 0.54 (95% CI: 0.42 to 0.70; $p < 0.0001$) in patients with diabetes,

0.62 (95% CI: 0.49 to 0.79; $p = 0.0001$) in patients with CKD, and 0.63 (95% CI: 0.51, 0.79; $p < 0.0001$) in patients with SBP < median (123 mm Hg) (Fig. 2).

Moreover the HR for the primary outcome (hospitalization for HF and/or cardiovascular death) in the eplerenone group as compared with the placebo group was 0.63 (95% CI: 0.44 to 0.89; $p = 0.009$) in patients in the lowest quartile of baseline SBP <25 percentile (<110 mm Hg), and 0.64 (95% CI: 0.48 to 0.84; $p = 0.001$) in patients with SBP between the lowest and median (110 and 123 mm Hg).

Discussion

The present findings show that eplerenone, started at a dose of 25 mg and carefully up-titrated to 50 mg (mean dose 40 mg) as tolerated, has a favorable benefit-risk profile in carefully selected and monitored patients, even if at increased risk of renal dysfunction, hyperkalemia and hypotension because of advanced age, diabetes, CKD, or low SBP. Specifically, the benefit of reduced incidence of cardiovascular death or HF hospitalization was preserved in all the high-risk subgroups studied without an increase in the risk of serious hyperkalemia and worsening renal function in any subgroup.

Older patients (≥ 75 years of age). Aldosterone levels decrease with age (7). However, aldosterone is not the only natural ligand of MR. Cortisol is a very potent agonist of MRs, but in physiological conditions, the enzyme 11 β HSD2 converts cortisol to cortisone, which does not activate the MR (8). Importantly, however, there is a decrease in the expression of this enzyme with age. Thus in the elderly, cortisol may be more active on MR in the vascular wall, renal tubule, and myocardium. There is also an increase in the expression of the MR with age in the vascular wall (9), which, in conjunction with the decrease in expression of 11 β HSD2, suggests that MR signaling may be as or more important in the elderly than in younger patients.

Clinicians may also be concerned about the safety of adding a MRA to an ACE-I or ARB and a BB in the elderly. It was therefore of interest to note that both the mean dose and the percentage of patients attaining the highest dose of eplerenone at the Month 5 visit was the same in older patients as in the overall EMPHASIS-HF study population. Similarly, the frequencies of the pre-specified safety outcomes were generally similar in older patients and in patients <75 years of age.

Diabetes mellitus. Diabetes mellitus is a major risk factor for the development of hyperkalemia (10) and renal failure. One postulated explanation for the increased risk of hyperkalemia in diabetes is hyporeninemic hypoaldosteronism. However, risks were not increased in diabetes (except modest hyperkalemia) suggesting that hyporeninemic hypoaldosteronism may be actually not quite common in diabetes. Excess hyperkalemia might just be due to the associated CKD.

Although the present data show that eplerenone is similarly beneficial in patients with diabetes than in those

without, Eplerenone does not reduce new onset of diabetes in this population (11).

It is therefore reassuring that eplerenone appeared to be well tolerated and safe in the selected and carefully monitored patients with diabetes in EMPHASIS-HF (38% of which had concomitant CKD).

Chronic kidney disease. Aldosterone-induced kidney injury is likely to be multifactorial, including its effect on systemic blood pressure, renal vasculature, local inflammation, and fibrosis (12). In addition to the traditional pathway, in renal tubular epithelial cells, activation of MR in nonepithelial tissues has been shown to cause hypertrophy and fibrosis (13).

Patients with HF-REF and concomitant CKD ($\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$) are at increased cardiovascular risk compared to those with preserved renal function, but they are less likely to be treated with renin-angiotensin-aldosterone system blockers or to receive the target dose of these agents. However, several studies and reviews highlighted the benefit of the addition of MRAs to ACE-I and/or ARB therapy in patients with proteinuric kidney disease to significantly reduce proteinuria, without causing significant hyperkalemia or worsening renal function (14,15). Furthermore, Vardeny *et al.* recently showed in a substudy of the RALES study that the absolute benefit of spironolactone was greatest in patients with reduced eGFR ($\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$) (16).

It was therefore especially reassuring that while there was an increase in the frequency of mild hyperkalemia (serum potassium $> 5.5 \text{ mmol/l}$) in patients randomized to eplerenone, there was also no significant increase in the frequency of serious hyperkalemia or WRF.

It is our view, therefore, that patients with HF-REF and concomitant CKD, meeting the inclusion and exclusion criteria of the EMPHASIS-HF study, should cautiously be given a trial of eplerenone beginning at a dose of 25 mg/day, with serial monitoring of serum potassium in an attempt to reduce the particularly high mortality and morbidity in these patients. It must, however, be emphasized that although this analysis was performed for patients with $\text{eGFR} < 60 \text{ ml/min/1.73 m}^2$, those with an $\text{eGFR} < 30 \text{ ml/min/1.73 m}^2$ and those with a baseline serum potassium $> 5.0 \text{ mmol/l}$ were excluded from the study. Furthermore, those with eGFR 30 to 49 ml/min/1.73 m^2 had a different and more cautious dosing regimen (eplerenone was started at a dose of 25 mg every other day and increased to 25 mg daily 4 weeks, provided the serum potassium was no more than 5.0 mmol/l).

SBP below median (<123 mm Hg). Hypotension is a particular concern in patients with HF-REF who often have an intrinsically low SBP and usually an indication for 3 or more BP-lowering drugs (17). These concerns are greatest in the elderly who are at risk of orthostatic hypotension leading to falls and loss of consciousness.

As in the other pre-specified high-risk subgroups in this analysis the use of eplerenone did not result in any

significant increase in the incidence of serious hyperkalemia or WRF. Interestingly there was no clinically significant decrease of SBP in those with SBP < median.

This experience with eplerenone 25 to 50 mg/daily in the various high-risk subgroups reported here is in contrast to that reported over the last several years from many centers who noted frequent intolerance of MRAs, in part related to a high incidence of hyperkalemia, acute renal failure, or both. For example after the RALES study (1), Juurlink et al. (18) noted an increased incidence of hospitalization for hyperkalemia in Ontario in patients with HF treated with spironolactone (patients were on average 13 years older than in the RALES study). More recently the TIME-CHF (the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure randomized trial) investigators (19) found that the use of spironolactone >25 mg/day in patients >60 years of age was associated with a more than 25% incidence of mild hyperkalemia (>5.5 mmol/l). A recent study from the Cleveland Clinic, evaluating the use of MRAs in patients admitted with HF after the results of EMPHASIS-HF (2), noted a high incidence (40%) of MRA (spironolactone in 90% of cases) discontinuation during hospitalization (20).

One explanation for the high incidence of hyperkalemia and/or WRF, as well as intolerance associated with the use of a MRA, in these patients is that many clinicians have used spironolactone in the dosing regimen used in RALES (12.5 to 50 mg/day) in patients with HF and mild symptoms such as those in the EMPHASIS-HF study (19,21). These doses may not be associated to the same risk/benefit than observed with eplerenone 25 to 50 mg in the EMPHASIS-HF study. Furthermore all these studies included both patients with HF with preserved ejection fraction, in whom MRAs were not recommended, as well as those with HF-REF. Importantly patients included in studies cited above were on average older, with more severe CKD (patients with eGFR <30 ml/min/1.73 m² were included in the TIME-CHF study) and received higher MRA doses than in the RALES or EMPHASIS-HF studies (22). Finally, patients may have also taken nonsteroidal anti-inflammatory agents, other potassium-sparing diuretics, and potassium supplements in these studies, drugs that increase the risk of developing serious hyperkalemia and/or WRF. Those patients were excluded from the EMPHASIS-HF study. Furthermore, patients included in the EMPHASIS-HF study, as in other trials cited previously, had to be on optimal ACE-I/ARB therapy before enrollment, which may have selected out a population less likely to have hyperkalemia or WRF secondary to MRA, as compared with unselected patients reported in observational registries. It is appropriate to emphasize that our conclusions are limited to the EMPHASIS-HF study type of patients and may not apply to the patients at the highest risk for complications who were excluded from the study. The subsets evaluated in the current analysis represent high-risk subgroups, which were not excluded by the entry criteria.

Importantly, surveillances of serum potassium and renal function were probably more closely made in patients included in the EMPHASIS-HF study than in “real-life” patients.

Study limitations. Based on the very low incidence rates of severe hyperkalemia (K >6.0 mmol/l) and the sample sizes, the comparisons within subgroups are underpowered, and therefore, type II error cannot be excluded and the lack of statistical significance should not be portrayed as categorical proof that patients on eplerenone have no difference in risk (either greater or smaller) than placebo patients. However, 2 subgroups showed a greater percentage for eplerenone and 2 showed a greater percentage for placebo.

Conclusions

The excellent benefit-to-risk ratio of eplerenone in the subgroups in this analysis at high risk for developing hyperkalemia and/or worsening renal function with an excellent safety and tolerance combined with a substantial reduction of the combined endpoint of cardiovascular mortality and hospitalization for HF, presents compelling evidence for its use in all patients with HF-REF meeting the inclusion and exclusion criteria of the EMPHASIS-HF study. Even so, serum potassium and renal function have to be carefully monitored in these patients strictly selected to benefit from MRAs.

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